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OTOLOGY SECTION

Recurrence in cholesteatoma surgery: what have we learnt and where are we going? A narrative review

Il colesteatoma ricorrente nella chirurgia dell'orecchio medio: lezioni imparate e prospettive future. Una narrative review

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SUMMARY

Treatment of cholesteatoma is surgical and has historically encompassed two main techniques: canal wall up (CWU) and canal wall down (CWD) tympanoplasty. Follow-up for cholesteatoma is still debated and can be either radiological or with second-look surgery. MRI with diffusion weighted sequences has proved to have high sensitivity and specificity in detecting recurrent or residual disease. Specifically, non-echo planar imaging DWI (non-EPI DWI) has been shown to be superior to other imaging techniques, allowing, in some cases, to avoid second-look surgery. Both residual and recurrence rates are higher in CWU compared to CWD procedures. Endoscopic ear surgery (EES) has become popular with the advantage of "looking around corners". The endoscope is used in addition to a microscope or exclusively to reduce cholesteatoma recurrence. In addition, it has been demonstrated that mastoid obliteration and the use of potassium titanyl phosphate laser (KTP) can reduce cholesteatoma recurrence, with better functional outcomes. A synthetic sulphur compound (MESNA) may have an interesting role in the overall improvement in recurrence and residual cholesteatoma disease. This narrative review critically appraises the factors associated with the risk of recurrent cholesteatoma.

KEY WORDS: cholesteatoma, recurrence, residual disease, diffusion weighted imaging, treatment outcome

RIASSUNTO

Il trattamento del colesteatoma è chirurgico e si basa su due tecniche principali: la timpanoplastica aperta e la timpanoplastica chiusa. Il follow up del colesteatoma può essere radiologico oppure mediante un secondo tempo chirurgico. La RM a diffusione nella diagnosi di colesteatoma ricorrente e residuo ha una sensibilità e specificità maggiore della TC. In particolare, la non-echo planar imaging DWI (non-EPI DWI) si è dimostrata superiore, consentendo in alcuni casi di non effettuare il secondo tempo chirurgico. In molti studi presenti in letteratura è stato osservato come il tasso di recidiva sia maggiore nella timpanoplastica chiusa rispetto a quella aperta. Inoltre, è stato dimostrato come l'obliterazione mastoidea e l'utilizzo del potassium titanyl phosphate (KTP) laser possano ridurre la recidiva di colesteatoma, con migliori outcomes funzionali. L'endoscopio può essere utilizzato in aggiunta al microscopio o in maniera esclusiva, in ottica di ridurre la ricorrenza del colesteatoma grazie alla capacità di "guardare dietro gli angoli". Un composto sintetico solforico (MESNA) sembra aver dimostrato un ruolo interessante nel migliorare i tassi di recidiva. Questa narrative review analizza in modo critico i fattori associati al rischio di colesteatoma ricorrente.

PAROLE CHIAVE: *colesteatoma, ricorrenza, residuo, RM in diffusione, trattamento e risultati*

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Introduction

Cholesteatoma is a chronic otitis of the middle ear cleft, which derives from an abnormal proliferation of a keratinising squamous epithelium [1]. It consists of two elements: acellular keratin debris, which forms the content of the sac, and the matrix, which forms the sac itself. The matrix is biologically active, producing proteolytic enzymes that are responsible for bone erosion [1]. Cholesteatoma can be congenital or acquired. The former is due to epidermal debris that remains intruded into the middle ear during embryogenesis [2]. The latter can be primary (if it arises from a retraction pocket) or secondary (if it develops as a result of an epithelial migration from a tympanic perforation, a trauma or otologic surgery) [2]. Diagnosis is based on clinical symptoms, otoscopic findings and imaging. Surgery is currently the only treatment that can achieve complete removal of the disease, with conservative management reserved for those patients with a contraindication to a general anaesthesia. The goals of surgery are widely accepted: primarily to obtain a safe and dry ear and secondarily to preserve, and potentially, restore hearing. Historically, the two main surgical techniques are canal wall down (CWD) and canal wall up (CWU). CWD is a technique in which the postero-superior bony canal wall is lowered, depending on the extent of the disease, in order to create an open mastoid cavity. An extension of this technique is the "radical" CWD mastoidectomy, which involves complete removal of the middle ear, including the sound transmission system, excluding the stapes, when present, and eradication of tubal function [3]. On the other hand, the CWU procedure implies the removal of all mastoid air cells along the tegmen and sigmoid sinus, with preservation of the posterior ear canal wall [4,5]. The main advantage of CWU is the preservation of natural anatomy of the external auditory canal (EAC), facilitating healing and avoiding cavity problems such as accumulation of debris and caloric vertigo [3]. CWU also facilitates fitting of hearing aids post-operatively, as reported in several articles in the literature [4-8]. Given the preservation of anatomical structures and the resulting conservation of middle ear resonance, it appears to be associated with better hearing outcomes [9,10], although several studies have failed to demonstrate a significant difference between the two approaches [4,11,12]. However, the CWU technique does not facilitate broad intra-operative visualisation of areas such as sinus tympani, supratubal recess, the attic, the posterior crus of stapes and facial recess. The implication is that residual disease is less easily detected compared to the CWD approach, increasing the rate of recurrence. The CWD procedure has the advantage of being able to visualise the cholesteatoma extensively, with complete en-bloc removal, thus ensuring surgical clearance [13]. The aim of this paper is to critically review the factors affecting the risk of recurrent cholesteatoma.

Cholesteatoma recidivism

A distinction must be made between recurrence and residual. Recurrence occurs when a new retraction pocket is formed from the tympanic membrane or the pars flaccida area. Risk factors involved in the formation of a new retraction pocket include age [14], mucosal preservation [15] and Eustachian tube (ET) function [16]. This process appears to be related to the re-aeration of the tympanic and mastoid cavity in the post-operative period [17]. It has been observed that poor aeration creates negative pressure in the middle ear cavity, thus predisposing to the formation of a retraction pocket. Other factors to consider are the integration of the reconstructed cartilage with the residual tympanic membrane and the healing process. Indeed, a study by Yazama et al. identified that the major sites of recurrence were the perimeter of the cartilage reconstruction and regions where the cartilage overlapped. In addition, persistent ET dysfunction may contribute to deformation of the reconstructed cartilage [18]. Residual cholesteatoma, on the other hand, occurs when the surgeon unintentionally leaves disease in the tympanic or mastoid cavity, either because of the poor exposure and visualisation of the surgical field or the anatomical location (e.g., tympanic sinus and facial recess [19] or because of excessive bleeding during the surgical procedure [20]). Tomlin et al. [6] carried out a meta-analysis on the risk of recurrence of cholesteatoma, reporting lower percentages of residual and recurrent disease after CWD (range 5% to 17%) compared to CWU surgery (range 9% to 70%). The relative risk of recurrent or residual disease was 2.87 (95% Confidence Interval: 2.45 to 3.37) after CWU compared to CWD.

In addition to the elected surgical technique and the pathophysiological factors described above, the risk for cholesteatoma recidivism can be influenced by other factors, such as the extent of the disease, cholesteatoma location and presentation of pre-operative ear discharge [21]. In several studies, a higher risk of recidivism has been shown in pars tensa cholesteatomas than in pars flaccida cholesteatomas [22]. The European Academy of Otology and Neurotology (EANO) and Japanese Otological Society (JOS) working group developed a staging system (EANO/JOS cholesteatoma classification system) that applies to 4 different categories of middle ear cholesteatoma: pars flaccida cholesteatoma, pars tensa cholesteatoma, congenital cholesteatoma and cholesteatoma secondary to a tensa perforation (Tab. I) [23].

Angeli et al. [24] attempted to evaluate the utility and prognostic capabilities of this staging system in predicting cholesteatoma recurrence. Although this staging allows a better description of the type and extent of pathology, also permitting a clearer and more standardised description of surgical outcomes, its prognostic value for cholesteatoma recurrence remains unproven.

Table I. EANOS/JOS classification and staging system [23].

Stage I	Localised cholesteatoma The site of cholesteatoma origin, i.e., the attic for pars flaccida cholesteatoma, the tympanic cavity for pars tensa cholesteatoma, congenital cholesteatoma, and cholesteatoma secondary to a tensa perforation
Stage II	Cholesteatoma involving two or more sites
Stage III	Cholesteatoma with extracranial complications or pathologic conditions includes: facial palsy, labyrinthine fistula: with conditions at risk of membranous labyrinth, labyrinthitis, postauricular abscess or fistula, zygomatic abscess, neck abscess, canal wall destruction more than half the length of the bony ear canal, destruction of the tegmen: with a defect that requires surgical repair, and adhesive otitis: total adhesion of the pars tensa
Stage IV	Cholesteatoma with intracranial complications Includes: purulent meningitis, epidural abscess, subdural abscess, brain abscess, sinus thrombosis, and brain herniation into the mastoid cavity

Revision surgery presents some major challenges, most notably being the distortion of normal anatomy and loss of anatomical landmarks. This leads to increased risks and complications during surgery and reliance upon highly experienced surgeons.

Key steps for successful surgery are confident identification of the facial nerve, labyrinth and the oval window. Granulation tissue must be removed completely, because it is a source of otorrhoea and because it may underly a cholesteatoma. The correct size of the meatoplasty is another key point: an inadequate meatoplasty may, in fact, not allow complete mastoid dominance and promote retention of keratin debris. It is important to emphasise that there is no single, correct procedure to follow; the choice must always be tailored to the patient [25].

CWD *vs* CWU: recurrence rate and quality of life

A debated issue between these two techniques is the post-operative quality of life (QoL). Historically, CWD has always been associated with worse quality of life due to the limitations of the neo-mastoid cavity [26]. However, recent studies show that there is no significant difference in QoL between CWU and CWD procedures [27,28]. In particular, a recent study by Lucidi et al. [29] compared the early and one year-post-operative results in CWD versus CWU without obliteration of the surgical cavity, demonstrating the absence of a significant difference in self-perceived quality of life. A significant limitation of this study is the short follow-up of only one year.

Mastoid obliteration

Mastoid obliteration entails the surgical elimination or reduction of the size of a mastoid cavity. It is usually performed during or following a CWD, but it can also be performed after CWU. It is a surgical technique that attempts to combine the advantages of CWU and CWD with the goal of reducing the incidence of residual disease and recurrence. The main limitation of the technique is the inability to explore the mastoid cavity during follow-up with the risk of developing a "silent cholesteatoma", making radiological follow-up essential. This technique has become popular in the last two decades with the development of non-EPI DW-MRI, which facilitates detection of cholesteatoma in obliterated or reconstructed cavities [30]. Surgical techniques and materials used for obliteration and reconstruction vary widely. The materials used can be autologous, allogenic, or synthetic. Among autologous materials, the most widely used is bone, harvested as pate or chips. It has the advantage of retaining its volume compared to soft tissue. Other materials used are cartilage from concha or tragus and soft tissue flaps, which may include fascia, periosteum and/or muscle. The most widely used flap is the middle temporal artery flap, which is very versatile and resists atrophy, which is the major weakness of muscle flaps. It is very important to be cautious when harvesting any graft material, especially with bone pate, to not inoculate microscopic epithelial cells, which could lead to a recurrence of cholesteatoma in the future. As far as synthetic materials are concerned, the most widely used is bioactive glass (BAG), followed by hydroxyapatite and titanium. The major complication of synthetic materials is extrusion. Choong et al. [31] in their review cited an extrusion rate of 3.6%, which is much higher in the case of hydroxyapatite. The latter material also makes revision surgery very complicated and increases the rate of infection. However, there is still no consensus around the technique, type of material to be used, or the ideal timing for surgery (simultaneous or during revision surgery) [32]. A systematic review and meta-analysis by Illes et al. [30] collected data from 2077 operations from 11 articles to evaluate the effectiveness of mastoid obliteration compared to the CWU technique. The results demonstrated that mastoid obliteration significantly reduced cholesteatoma recidivism (Odds Ratio = 0.45, Confidence Interval = 0.26-0.8, p = 0.014). Furthermore, no difference in outcome was demonstrated using different materials for mastoid obliteration and posterior wall reconstruction.

Endoscopic ear surgery (EES): an adjunct or an alternative to microscopic surgery

Since the 1950s, microsurgery has been considered the traditional surgical technique for chronic cholesteatomatous otitis media. However, in recent decades, the application of the endoscope to otological surgery, with the advantage of "looking around corners", has become popular. The microscope offers a magnified and illuminated surgical field, allowing two handed surgery, binocular vision and depth perception. However, the limitation of a straight line vision creates blind spots, or hidden areas that are difficult to reach during surgery [33]. Endoscopic ear surgery (EES), on the other hand, using angled endoscopes (30 and 45°) offers a clear visualisation of hidden areas of retrotympanum, anterior epitympanum, facial recess, and sinus tympani. It is also considered a minimally invasive technique, using the transcanal approach, avoiding retroauricular incision [34]. In middle ear surgery, the use of endoscopes can be classified in: A) assisted, in which the endoscope is used exclusively to search for residual cholesteatoma after the microsurgical approach; B) mixed, in which microscope and endoscope are both used for surgical cholesteatoma eradication; C) exclusive endoscopic or TEES (Transcanal Endoscopic Ear Surgery).

Endoscopes are frequently used in cholesteatoma surgery only as an adjunct to the microscope for diagnostic purposes. Exclusive endoscopic surgery has not gained widespread acceptance for several reasons: only one hand can be used for surgical manoeuvres, lack of depth perception, difficulty to perform ossicular reconstruction, frequent fogging and smearing of endoscopic tip and the risk of thermal injury to the facial nerve, chorda tympani and cochlear promontory with transmitted heat of the endoscope tip [35]. The indications for EES in cholesteatoma treatment are limited to the tympanic space and its subsites (epitympanum, mesotympanum, retrotympanum, protympanum and hypotympanum). When the cholesteatoma involves the mastoid, the use of EES is controversial: some suggest switching to a traditional technique with microscope or a combined endoscopic and microscopic approach [36]. Others believe that the exclusive use of the endoscope is still possible in a small number of cases [37].

Various studies have shown that the EES has significantly reduced the residual and recurrence rate of cholesteatoma compared to microscope use alone, especially for CWU procedures. The commonest site of residual disease is the sinus tympani, even in second-look procedures [38]. A review by Hu et al. [39] demonstrated a recurrence rate in the EES approach between 0% and 10.5%, significantly lower than CWU approach, but similar to the CWD approach in an adult population**.** In addition, EES has shown a high rate of ossicular chain preservation, ranging from 24 to 33,3% due to a better visualisation of ossicles, preventing their unnecessary removal.

A review by Verma et al. [38] of 13 studies demonstrated that in 15.82% cases residual cholesteatoma was identified by using an endoscope after microscopic surgery. In three (Tarabichi [40] Migirov [41] and Barakate [42]), exclusive EES was performed with a rate of recidivism ranging from 0% to 20.6%. A limitation of these studies is the short mean follow-up (43, 12 and 16 months, respectively). Marchioni et al. [43,44] presented a study that started in 2005 and finished in 2015 in which 244 ears in 234 patients were treated with exclusive endoscopic approach (n = 144) or a combined approach with mastoidectomy (n = 100) for middle ear cholesteatoma, with at least 3 years of follow-up. In all, 30% of patients had an exclusively attic cholesteatoma, 17% an extension to mesotympanum, 15% an exclusively mesotympanic disease, 30% an antrum extension and 7% had mastoid involvement. Residuals were defined CT usually performed after 1 year of follow-up or during a planned surgical second-look. Recidivism rate was 32%, with recurrence and residual rates, respectively, of 12% and 20%. Studies that compared EES to a microscopic control group for cholesteatoma showed equivalent residual and recurrent rates, with no significant differences in hearing outcomes [45]. The microscope and endoscope are both useful tools in otological surgery, and are not in opposition but complementary. There is no ideal surgical technique; the most correct surgical technique should consider the extent of the disease, the patient's age and desire.

Laser in the treatment of cholesteatoma: a way to reduce residual disease?

The use of lasers in the treatment of cholesteatoma has become widespread in the last 2 decades, especially in the U.S. The most widely used laser in the treatment of cholesteatoma is the potassium titanyl phosphate (KTP) laser at 532 nm wavelength. Its strengths are the possibility of being transmitted via a hand-held semi-flexible fibre-optic cable, which can reach relatively inaccessible recesses of the middle ear, and its wavelength is absorbed by red pigments such as haemoglobin. At this wavelength, blood-containing structures are preferentially denatured, vaporised or heated by the laser, whereas non-blood containing structures, such as perilymph, have relatively little penetration. The use of the KTP laser allows atraumatic removal of cholesteatoma from the middle ear and ossicular chain, and precise haemostatic removal of diseased tissue such as polyps, granulations and adhesions. Retrospective studies have shown that the risk of residual cholesteatoma is reduced by half [46]. An important prospective study was conducted by Hamilton et al. [47] in two different hospitals, in which the same

surgeon operated using the KTP laser at one location and in the other without. All patients included in the study were required to undergo a second surgical procedure with full exposure of the middle ear and mastoid, including the entire bed of the previous cholesteatoma. This study showed that 1 of 36 patients with procedures utilising the KTP laser had residual disease, compared to 10 of 33 patients without KTP laser [47]. The primary risk of laser use is thermal collateral damage to exposed structures including the cochlea and the facial nerve. However, recent data observe that the rate of facial nerve paralysis is 0.6%, demonstrating that laser use appears safe if appropriate safety guidelines are followed [48]. Lasers seem to play an increasing role in EES thanks to the better bleeding control that can be challenging with one hand, and the atraumatic dissection of cholesteatoma, especially on the ossicular chain. Laser-assisted endoscopic cholesteatoma surgery showeda recurrence and residual rate between 0% and 19%, and not inferior to standard middle ear surgery [49]. Sharma et al. [50] presented a study based on a large paediatric population treated with purely endoscopic KTP laser resection for cholesteatoma over an eight-year period. Of the 83 patients included in this study with cholesteatoma confined to the middle ear and attic, 70 were treated with KTP laser. Residual disease was detected in 4 patients (6%). In 3 residual disease was found close to the facial nerve area that was spared from KTP laser application in order to avoid thermal injury. In conclusion, KTP laser has been shown to reduce the risk of residual cholesteatoma and is suggested to be beneficial to preserve ossicular function and safe hearing outcomes.

Imaging and recurrence

The most widely used radiological examination in the primary diagnosis of cholesteatoma is CT, demonstrating high sensitivity but low specificity [51]. In the case of residual or recurrent cholesteatomas, the sensitivity and specificity of CT drops dramatically given the difficulty in distinguishing changes due to previous surgery against bone erosion due to cholesteatoma [52]. In this scenario, the specificity of CT is 48%, while the sensitivity is 43% [53]. These difficulties are overcome in part by using diffusion weighted magnetic resonance imagining (DWI-MRI). Cholesteatoma appears to have a high signal intensity, mainly attributable to its water content and restricted water diffusion. In particular non-echo planar imaging DWI techniques allow less image distortion, lower artifacts than other DWI techniques and better identification of small lesions, reducing the false-positive rate (the sensitivity and specificity of Non EPI DWI-MRI are 89.79% and 94.57%, respectively) [54]. The use of DWI MRI in the diagnosis of residual or recurrent cholesteatomas may therefore be a viable alternative to routine second-look surgery in some cases [55].

Paediatric cholesteatoma

Paediatric cholesteatoma is much debated in the literature as there are different interpretations on its behaviour and surgical treatment. Some authors believe that cholesteatoma in children has a more aggressive growth pattern compared to adults, which leads to a higher incidence of both residual and recurrent disease. This behaviour would appear to be related to several factors: well-pneumatised mastoids in children allow for more extensive disease compared with more sclerotic mastoid bones in adults [9]; Eustachian tube anatomy and dysfunction predispose children to more frequent infections and retraction pockets [9]; a higher rate of keratinocyte proliferation and a pronounced inflammatory response of the peri-matrix and matrix in the paediatric population [56-59]. Despite all these theories, there are still many controversies, both on cholesteatoma behaviour and management. Indeed, there are currently no studies in the literature expressing a clear consensus on the surgical treatment of paediatric cholesteatoma. Both CWD and CWU procedures are used: some authors are in favour of CWU technique [60,61], others prefer CWD approach [62,63]. A third group is in favour of both procedures, recommending individualised treatment [64-66]. The main purposes of surgery in paediatric patients remain the eradication of cholesteatoma and restoration of hearing function: the balance between these two goals is related to the incidence of recidivism and degree of ossicular damage [67]. A recent analysis of the literature [68] showed that CWU is characterised by an average residual disease of approximately 15% (range 3.8%-21%), while CWD is associated with an average residual and recurrent cholesteatoma rates of 6.5% (range 0%-11.4%) and 5.1% (range 0%-18.4%), respectively [10,11,66,69-72]. These data showed that a staged approach to cholesteatoma is not necessarily more effective in reducing the rate of recidivism. In particular, CWD still represents the most efficient approach in eradication of tympano-mastoid cholesteatoma, with residual and recurrence rates close to 5%. In the light of the above-mentioned data, surgical treatment should be individualised, considering the extent of the disease and the conditions of the mucosal and ossicular chain [69]. The management of paediatric cholesteatoma is difficult for multiple reasons and children can sometimes be difficult to monitor clinically. If we consider the longevity of this part of population, it is mandatory to optimise the surgical management and monitoring of these patients.

The prognostic role of cell proliferation markers in recurrent cholesteatoma

Many studies have investigated the pathogenesis of cholesteatoma and the factors leading to cell proliferation and bone resorption. These include specific cytokeratins, inflamma-

tion, enzymes and local pressure. In particular, an altered receptor activator of nuclear factor-kappa B ligand (RANKL)/ Osteoprotegerin (OPG) protein ratio suggests the main role of RANKL/OPG pathway in the inflammation related to the growth of cholesteatoma, and osseous destruction due to middle ear cholesteatoma. Given the high proliferative rate of cholesteatoma and the tendency for recurrence, many studies have been conducted to find specific markers involved in the pathophysiology of this disease. Araz et al. [73] investigated the possible correlation between the cell proliferation markers Ki-67 and proliferating cell nuclear antigen (PCNA) with cholesteatoma recurrence. Ki-67 is a factor involved in proliferative cells, as it is essential in the G1, S, M and G2 phases (it is absent in G0) [74,75]. PCNA is a co-factor of DNA polymerase delta that participates in cell- proliferation [76]. The rate of Ki-67 and PCNA has been analysed in two groups of patients undergoing CWD surgery: with recurrent cholesteatoma and non-recurrent cases after at least 2 years of follow-up. The results did not demonstrate a significant difference between the two groups examined. Therefore, it appears that these two markers do not have a predictive role in cholesteatoma recurrence. However, given the high level of Ki-67 found in cholesteatoma cases with malleus erosion, it could be considered as an indicator of a destructive pattern of disease.

The promising role of MESNA (sodium 2-mercaptoethanesulphonate)

Sodium 2-mercaptoethanesulphonate, also known as MESNA, deserves brief mention. It is a synthetic sulphur compound that belongs to a class of thiols that produce mucolysis by disrupting disulphide bonds of the mucous polypeptide chains. It has been used in several diseases as a cytoprotective agent. Many studies *in vivo* and *in vitro* suggest that MESNA plays an important role as an antioxidant drug. Only in recent years has MESNA gained attention for its potential application in facilitating surgical dissection, leading to the concept of "chemically assisted dissection". The fundamental principle of chemically-assisted dissection lies in the rich disulphide bonds of the adhesions between the different tissue layers. In ENT surgery, topical MESNA has been used from ear and skull base to head and neck diseases. A review including 5 retrospective studies showed overall improvement in recurrence and residual cholesteatoma disease after MESNA application during surgery [77,78]. Further studies are needed to confirm these interesting findings.

Conclusions

Cholesteatoma is a disease with an intrinsic tendency to recidivism and its management is challenging. It remains a surgical disease, with a surgical skillset being a critical determinant in rates of recidivism. The emergence of EES and the use of laser have opened up new surgical methods to improve surgical outcomes and prognosis, with strengths and limitations. However, there is currently no gold standard surgical technique, as treatment must be tailored based on the extent of disease and middle ear condition.

Mastoid obliteration combines the advantages of CWU and CWD, reducing the recidivism rate compared to CWU. The use of lasers in cholesteatoma surgery is becoming popular due to the greater preservation of the ossicular chain and a safe hearing outcome, with promising studies demonstrating an improved recidivism rate.

The use of non-EPI DWI MRI has proved to have high sensitivity and specificity in detecting recurrent or residual disease, and is emerging as an alternative to routine second-look surgery.

Even if the near future will probably still see surgery having a crucial role in the management of this pathology, new technological tools (intra-operative imaging guidance, robot) and medical therapies will hopefully improve outcomes in the treatment of cholesteatoma in order to win this "eternal ear fight".

Conflict of interest statement

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Ethical consideration

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